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NOVEL BENZOTHIEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

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# NOVEL BENZOTHIEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

This application is a continuation in part of US application 08/305526 filed September 12, 1994, now pending.

## BACKGROUND OF THE INVENTION

This invention relates to novel benzothiepines, derivatives and analogs thereof, pharmaceutical compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as is associated with atherosclerosis, or hypercholesterolemia, in mammals.

It is well-settled that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly atherosclerosis. Interfering with the circulation of bile acids within the lumen of the intestinal tract is found to reduce the levels of serum cholesterol in a causal relationship. Epidemiological data has accumulated which indicates such reduction leads to an improvement in the disease state of atherosclerosis. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties," Biochimica et Biophysica Acta, 1210 (1994) 255-287 discusses the biochemistry, physiology and known active agents surrounding bile acids and cholesterol.

Pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic circulation of bile acids in humans by Heubi, J.E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport", Gastroenterology,1982:83:804-11.

In fact, cholestyramine binds the bile acids in the intestinal tract, thereby interfering with their normal enterohepatic circulation (Reihnér, E. et al, in "Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-CoA reductase activity and low density lipoprotein receptor expression in gallstone patients", Journal of Lipid Research, Volume 31, 1990, 2219-2226 and Suckling el al, "Cholesterol Lowering and bile acid

excretion in the hamster with cholestyramine treatment", Atherosclerosis, 89(1991) 183-190). This results in an increase in liver bile acid synthesis by the liver using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol levels.

In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with specific transport inhibitors (Kramer, et al, "Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, Vol. 268, No. 24, Issue of August 25, pp. 18035-18046, 1993).

In a series of patent applications, eg Canadian Patent Application Nos. 2,025,294; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 379 161; 0 549 967; 0 559 064; and 0 563 731, Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including bile acid, which inhibit the physiological bile acid transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as hypocholesterolemic agents.

In vitro bile acid uptake inhibition is disclosed to show hypolipidemic activity in The Wellcome Foundation Limited disclosure of the world patent application number WO 93/16055 for "Hypolipidemic Benzothiazepine Compounds"

Selected benzothiepines are disclosed in world patent application number WO93/321146 for numerous uses including fatty acid metabolism and coronary vascular diseases.

Other selected benzothiepines are known for use as hypolipaemic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed by application Nos. EP 508425, FR 2661676, and WO 92/18462, each of which is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclo benzothiepine ring.

The above references show continuing efforts to find safe, effective agents for the prophylaxis and treatment of hyperlipidemic

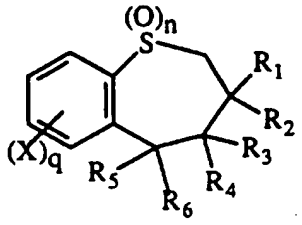
diseases and their usefulness as hypocholesterolemic agents.

Additionally selected benzothiepines are disclosed for use in various disease states not within the present invention utility. These are EP 568 898A as abstracted by Derwent Abstract No. 93-351589; WO 89/1477/A as abstracted in Derwent Abstract No. 89-370688; U.S. 3,520,891 abstracted in Derwent 50701R-B; US 3,287,370, US 3,389,144; US 3,694,446 abstracted in Derwent Abstr. No. 65860T-B and WO 92/18462.

The present invention furthers such efforts with novel benzothiepines, pharmaceutical compositions and methods of use therefor.

## SUMMARY OF THE INVENTION

The present invention is for a compound of the formula (I)



I

wherein q is an integer of from 1 to 4;

n is independently an integer of from 0 to 2.

$R_1$ and $R_2$ are independently H, $C_{1-10}$ alkyl or $R_1$ and $R_2$ taken together form $C_3$-$C_{10}$ cycloalkyl, preferably wherein both $R_1$ and $R_2$ cannot be hydrogen;

$R_3$ and $R_4$ are independently H, alkyl, aryl, OR, NRR', $S(O)_nR$, or $R_3$ and $R_4$ together form =O, =NOH, =S, =NNRR', =NR", =CRR' where R, R' and R" are selected from H, alkyl, alkenylalkyl, alkynylalkyl, aryl, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, or cyanalkyl; and provided that both $R_3$ and $R_4$ cannot be OH, $NH_2$ and SH;

$R_5$ is selected from alkyl, aryl, heterocycle, OR, NRR', $S(O)_nR$ wherein the alkyl, aryl, and heterocycle are each optionally substituted with alkyl, alkenyl, alkynyl, halogen, OR, NRR', $S(O)_nR$, $NO_2$, haloalkyl, carboxy, carboalkoxy, CN, or N+RR'R"Y- wherein R,

R' and R" are each independently as defined above, and Y is independently an anion, with the proviso that $R_5$ cannot be OH, $NH_2$, NRR'or N+RR'R"Y- when $R_1$, $R_2$, $R_3$, $R_4$, and $R_6$ are all hydrogen or R and R' are hydrogen or $C_1$-$C_6$ alkyl; with further proviso that when $R_5$ and $R_6$ are both hydrogen or when $R_5$ is hydrogen and $R_6$ is hydroxy, $R_1$, $R_2$, $R_3$, and $R_4$ cannot be all hydrogen and preferably when either $R_5$ or $R_6$ is NRR', then $R_3$ or $R_4$ cannot be aryl;

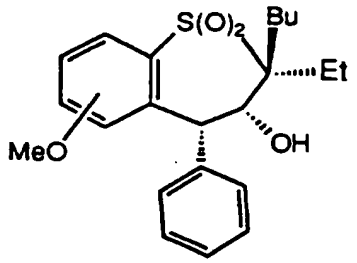
$R_6$ is selected from hydrogen or $R_4$ and $R_6$ together form -O-, or $R_5$ and $R_6$ together form a $C_3$-$C_{10}$ cycloalkylidine; with the proviso that $R_4$ and $R_6$ can not together be -O- when $R_3$ is OH, $NH_2$ or SH or when $R_1$, $R_2$, $R_3$ and $R_5$ is hydrogen;

X is selected from H, alkyl, alkenyl, alkynyl, halogen, OH, $NH_2$, OR, NRR', NROR', $S(O)_nR$, $NO_2$, haloalkyl, carboxy, carboalkoxy, CN, or N+RR'R"Y- wherein R, R' and R" are each independently defined as above and Y is independently an anion; or pharmaceutically acceptable salt, solvate or prodrug thereof.

Preferred compounds include compounds of formula I wherein $R_1$ and $R_2$ cannot both be hydrogen;

Preferred compounds also include compounds of formula I wherein when either $R_5$ or $R_6$ is NRR', then $R_3$ or $R_4$ cannot be aryl.

The more preferred compounds are of the formula I wherein $R_1$ is butyl, $R_2$ is ethyl, $R_3$ is hydrogen, $R_4$ is hydroxy, $R_5$ is phenyl, q is 0, n is 2, and X is methoxy as shown below, or hydroxylamino or amino wherein each of $R_2$, $R_4$ and $R_5$ are in the same stereo relationship to the ring system which may be depicted as follows:




The present invention is also a pharmaceutical composition

for the prophylaxis or treatment of a disease or condition for which a bile acid uptake inhibitor is indicated, such as hyperlipidemic condition, and in particular atherosclerosis, which comprises a compound of the formula I in an amount effective for inhibiting the bile acid uptake or the prophylaxis or treatment of the disease or condition benefitted thereby and a pharmaceutically acceptable carrier.

The present invention is also a method of treating a disease or condition in humans for which a bile acid uptake inhibitor is indicated which comprises a compound of the formula I in unit dosage form.

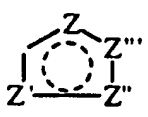
The present invention is also a process for the preparation of a compound of formula I.

.DETAILED DESCRIPTION

"Alkyl", "alkenyl" and "alkynyl" unless otherwise noted are each of from one to six carbons for alkyl or two to six carbons for alkenyl and alkynyl in the present invention and, therefore, means methyl, ethyl, propyl, butyl, pentyl or hexyl and ethenyl, propenyl, butenyl, pentenyl, or hexenyl and ethynyl, propynyl, butynyl, pentynyl, or hexynyl respectively and isomers thereof. When each of these groups is referred to as a moiety in a parent molecule, such as alkenylalkyl, these definitions also apply.

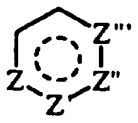
"Aryl" is phenyl or naphthyl.

"Heterocyclo" is one of the following:




(i)

or




(ii)

wherein Z, Z', Z'' or Z''' is C, S, O, or N, with the proviso that one of Z, Z', Z'' or Z''' is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z', Z'' or Z''' only when each is C.

The halo group meant by "halogen" or meant in haloalkyl is a

fluoro, chloro, bromo or iodo group.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulphonic and sulphuric acids, and organic acids, such as acetic, benzenesulphonic, benzoic, citric, ethanesulphonic, fumaric, gluconic, glycollic, isothionic, lactic, lactobionic, maleic, malic, methansulphonic, succinic, -- toluenesulphonic, tartaric and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, and alkaline earth salts, such as magnesium and calcium salts.

The anions of the definition of Y in the present invention are, of course, also required to be pharmaceutically acceptable and are also selected from the above list.

"Prodrug" is a physiologically functional derivative of a compound of the present invention, for example, an ester, wherein the pharmacologic action of the compound results from conversion by metabolic processes within the body. In other words, such biotransformation upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) the compound or an active metabolite thereof. These prodrugs may or may not be active in their own right.

The compounds of the formula I may have at least two asymmetrical carbon atoms and therefore include rotational isomers. The invention includes all possible stereoisomers, in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials or by separating isomers of a compound of formula I.

Isomers may include geometric isomers, e.g. when $R_1$ contains a double bond. All such isomers are contemplated for this invention.

In other words, diastereoisomers, enantiomers, racemates and tautomers are contemplated by the present invention.

The compounds of the formula I as referred to in the compositions and methods of use of the present invention are meant to include their salts, solvates and prodrugs as defined herein.

The term "a bile acid uptake inhibitor" as used in the present invention refers to inhibition of absorption of bile acids from the intestine of a mammal, such as a human, and includes increasing the fecal excretion of bile acids in a mammal, such as a human, as well as reducing the blood plasma or serum concentrations of cholesterol and cholesterol ester and more specifically reducing LDL and VLDL cholesterol in a mammal, such as a human. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid uptake inhibition are, for example a hyperlipidemic condition, such as atherosclerosis.

The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

Generally, the compounds of the formula I can be prepared in one of the following procedures.

The compounds in this invention can be synthesized by the route shown in scheme 1.

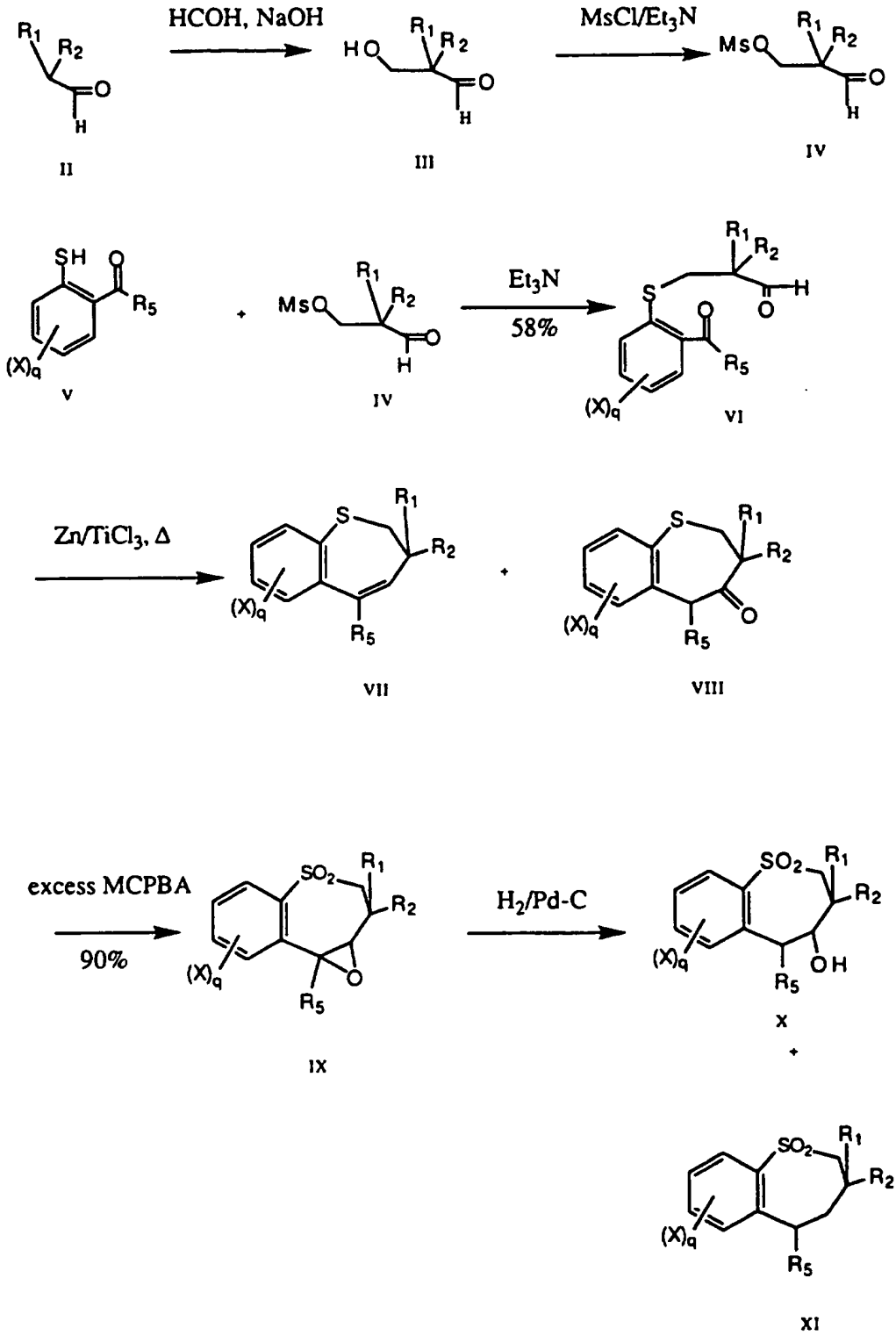
Reaction of aldehyde II with formaldehyde and sodium hydroxide yields the hydroxyaldehyde III which is converted to mesylate IV with methansulfonyl chloride and triethylamine similar to the procedure described in Chem. Ber. **98**, 728-734 (1965). Reaction of mesylate IV with thiophenol V, prepared by the procedure described in WO 93/16055, in the presence of triethylamine yields keto-aldehyde VI which can be cyclized with the reagent, prepared from zinc and titanium trichloride in refluxing ethylene glycol dimethyl ether (DME), to give a mixture of 2,3-

dihydrobenzothiepine VII and two racemic steroisomers of benzothiepin-(5*H*)-4-one VIII when $R_1$ and $R_2$ are nonequivalent.

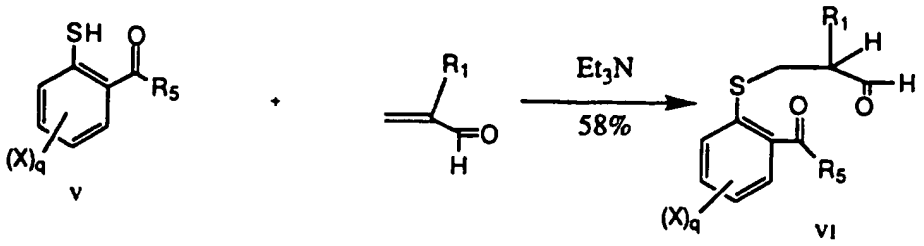
Oxidation of VII with 3 equivalents of m-chloroperbenzoic acid (MCPBA) gives isomeric sulfone-epoxides IX which upon hydrogenation with palladium on carbon as the catalyst yield a mixture of four racemic stereoisomers of 4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides X and two racemic stereoisomers of 2,3,4,5-tetrahydro-benzothiepine-1,1-dioxides XI when $R_1$ and $R_2$ are nonequivalent.

Optically active compounds of this invention can be prepared by using optically active starting material III or by resolution of compounds X with optical resolution agents well known in the art as described in *J. Org. Chem.*, **39**, 3904 (19740, *ibid.*, **42**, 2781 (1977), and *ibid.*, **44**, 4891 (1979)

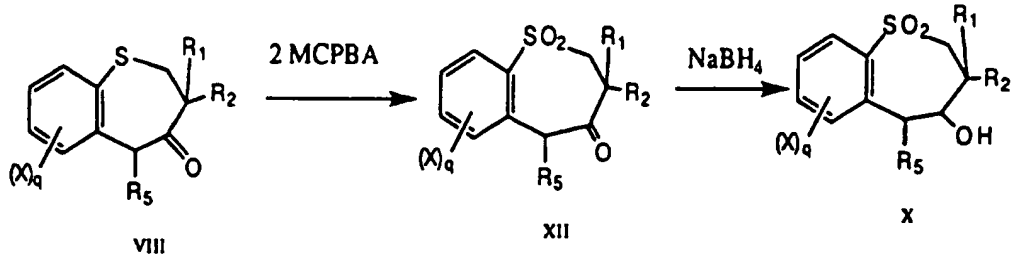
Scheme 1

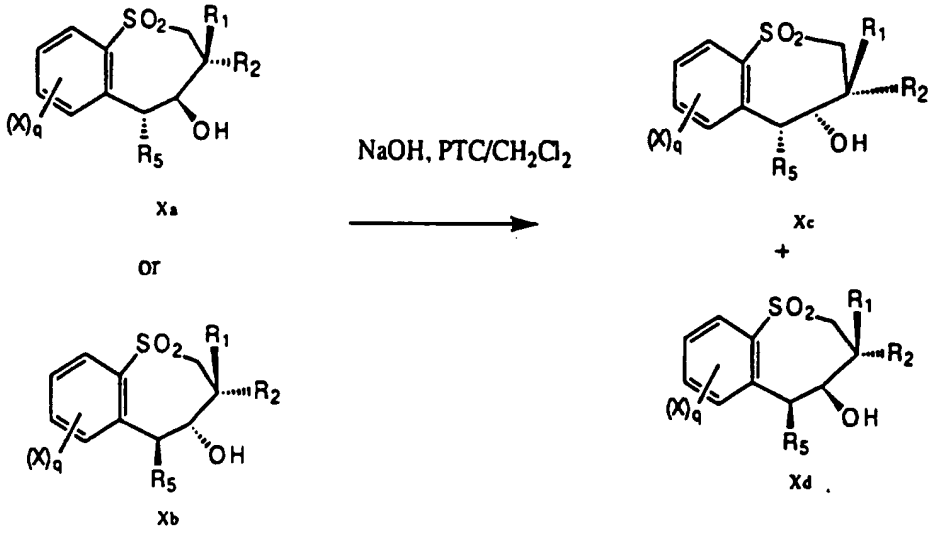

HCOH, NaOH
MsCl/Et3N
Et3N
58%
Zn/TiCl3, Δ
excess MCPBA
90%
H2/Pd-C
II
III
IV
V
VI
VII
VIII
IX
X
XI

Alternatively, keto-aldehyde VI where $R_2$ is H can be prepared by reaction of thiophenol V with a 2-substituted acrolein.




Benzothiepin-(5*H*)-4-one VIII can be oxidized with MCPBA to give the benzothiepin-(5*H*)-4-one-1,1-dioxide XII which can be reduced with sodium borohydride to give four racemic stereoisomers of X. The two stereoisomers of X, Xa and Xb, having the OH group and $R_5$ on the opposite sides of the benzothiepine ring can be converted to the other two isomers of X, Xc and Xd, having the OH group and $R_5$ on the same side of the benzothiepine ring by reaction in methylene chloride with 40-50% sodium hydroxide in the presence of a phase transfer catalyst (PTC). The transformation can also be carried out with potassium t-butoxide in THF.




when $R_1$ = Bu, $R_2$ = Et, $R_5$ = Ph, X = H, q = 4

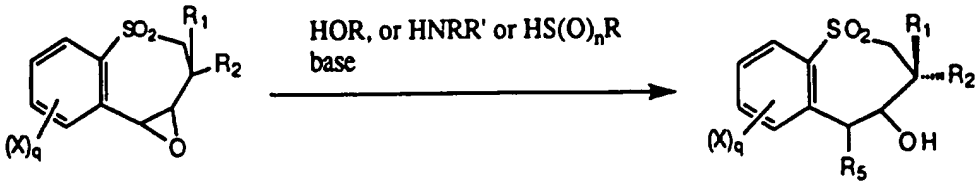
6a = Xa

6b = Xb

6c = Xc

6d = Xd

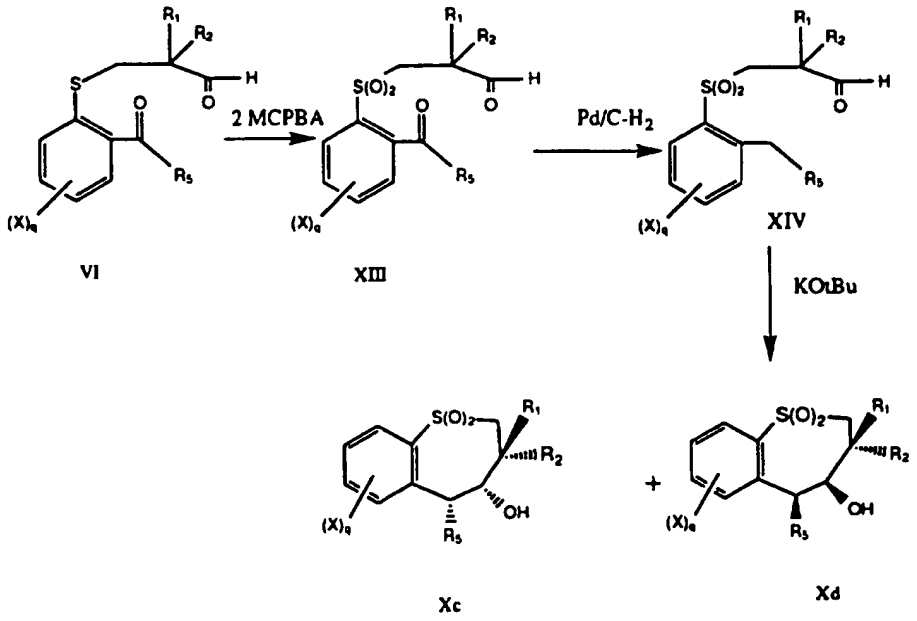
The compounds of this invention where $R_5$ is OR, NRR' and $S(O)_nR$ and $R_4$ is hydroxy can be prepared by reaction of epoxide IX where $R_5$ is H with thiol, alcohol, and amine in the presence of a base.




$R_5$ = OR, NRR', $S(O)_nR$

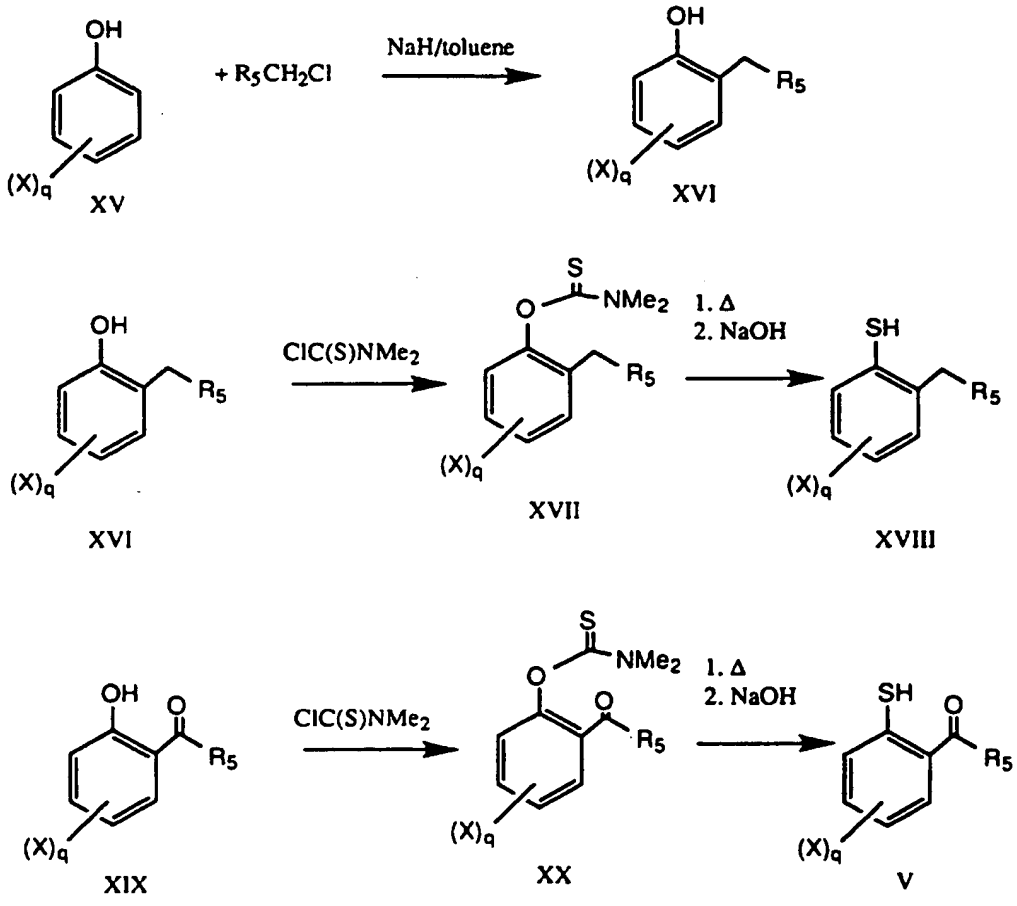
Another route to Xc and Xd of this invention is shown in scheme 2. Compound VI is oxidized to compound XIII with two equivalent of m-chloroperbenzoic acid. Hydrogenolysis of compound XIII with palladium on carbon yields compound XIV which can be cyclized with either potassium t-butoxide or sodium hydroxide under phase transfer conditions to a mixture of Xc and Xd. Separation of Xc and Xd can be accomplished with either HPLC or fractional crystallization.

Scheme 2



The thiopenols XVIII and V used in this invention can also be prepared according to the scheme 3. Alkylation of phenol XV with an arylmethyl chloride in nonpolar solvent according to the procedure in ***J. Chem. Soc.*, 2431-2432 (1958)** gives the ortho substituted phenol XVI. The phenol XVI can be converted to the thiophenol XVIII via the thiocarbamate XVII by the procedure described in ***J. Org. Chem.*, 31, 3980 (1966)**. The phenol XVI is first reacted with dimethyl thiocarbamoyl chloride and triethylamine to give thiocarbamate XVII which is thermal rearranged at 200-300 °C and the rearranged product is hydrolyzed with sodium hydroxide to yield the thiophenol XVIII. Similarly, Thiophenol V can also be prepared from 2-acylphenol XIX via the intermediate thiocarbamate XX.

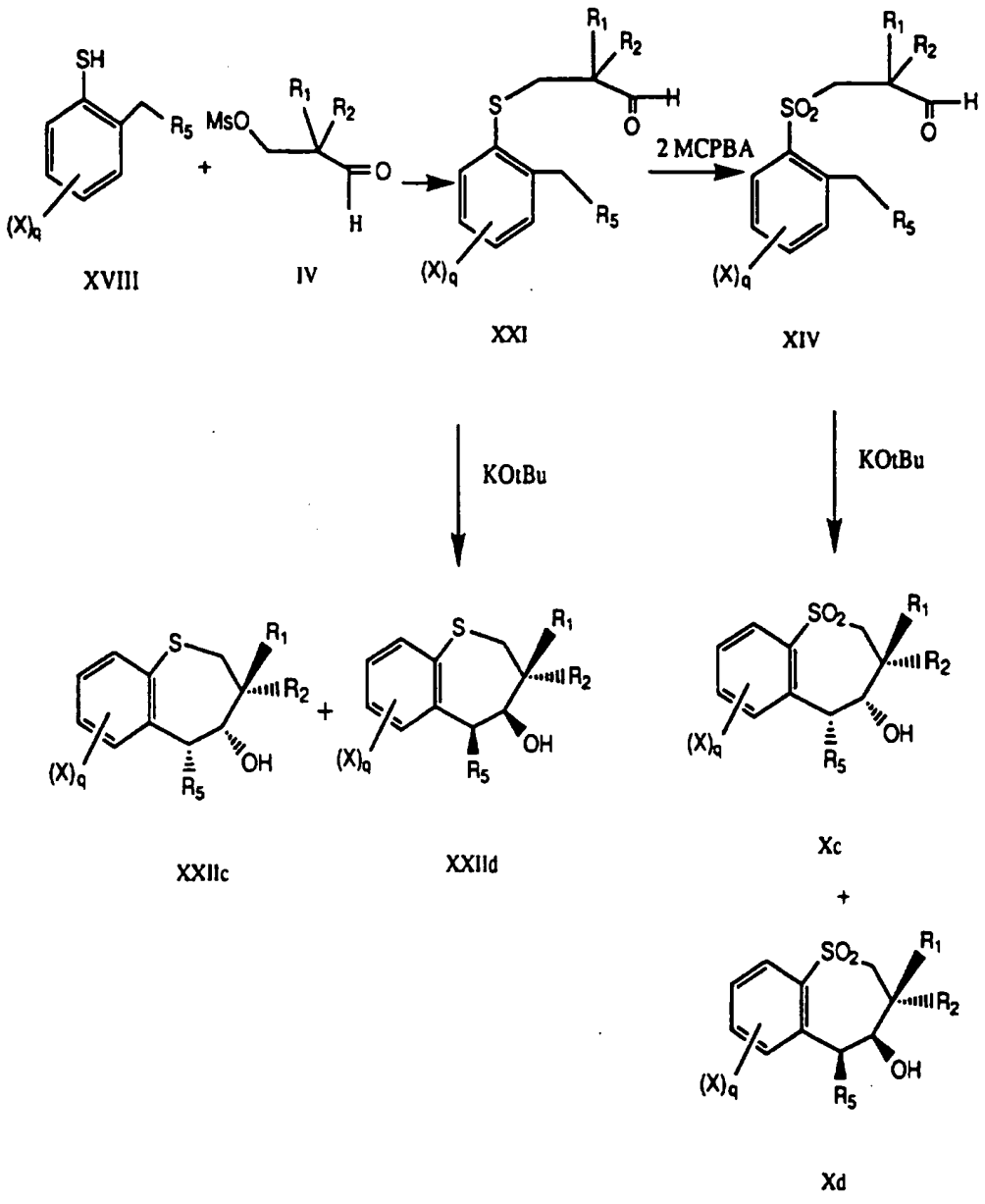
Scheme 3




Scheme 4 shows another route to benzothiepine-1,1-dioxides Xc and Xd starting from the thiophenol XVIII. Compound XVIII can be reacted with mesylate IV to give the sulfide-aldehyde XXI. Oxidation

of XXI with two equivalents of MCPBA yields the sulfone-aldehyde XIV which can be cyclized with potassium t-butoxide to a mixture of Xc and Xd. Cyclyzation of sulfide-aldehyde with potassium t-butoxide also gives a mixture of benzothiepine XXIIc and XXIId.

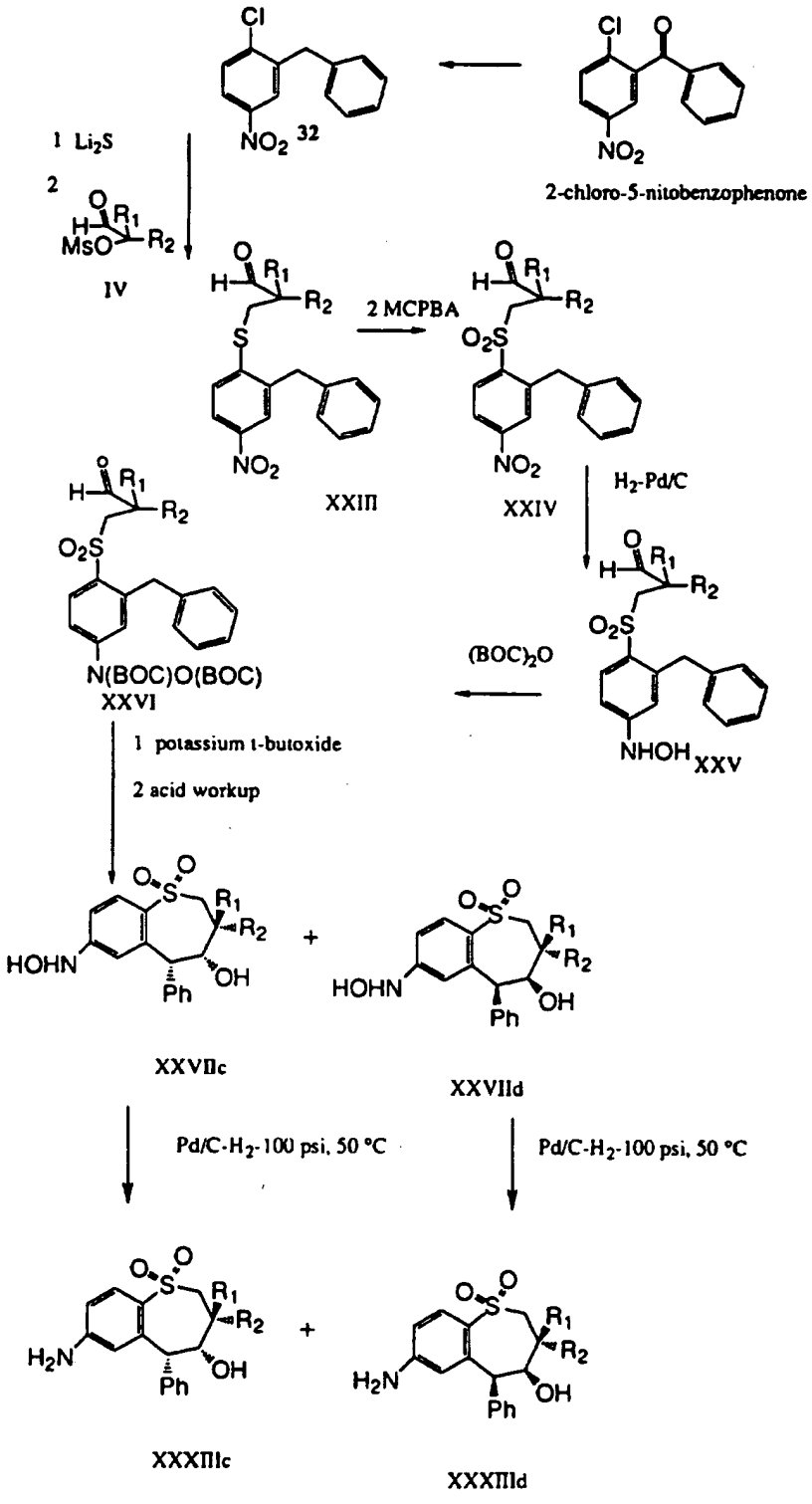
Scheme 4




Examples of amine and hydroxylamine containing compounds of this invention can be prepared as shown in scheme 5 and scheme 6. 2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane

32. Reaction of 32 with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV which can be reduced by hydrogenation to the hydroxylamine XXV. Protecting the hydroxylamine XXV with di-t-butyldicarbonate gives the *N,O*-di-(t-butoxycarbonyl)hydroxylamino derivative XXVI. Cyclization of XXVI with potassium t-butoxide and removal of the t-butoxycarbonyl protecting group gives the a mixture of hydroxylamino derivative XXVIIc and XXVIId. The primary amine XXXIIIc and XXXIIId derivatives can also be prepared by further hydrogenation of XXIV or XXVIIc and XXVIId.

Scheme 5


Cl
NO2 32
Cl O
NO2
2-chloro-5-nitobenzophenone
1 Li2S
2
MsO
IV
2 MCPBA
XXIII
XXIV
H2-Pd/C
(BOC)2O
N(BOC)O(BOC)
XXVI
XXV
NHOH
1 potassium t-butoxide
2 acid workup
HOHN
Ph
OH
XXVIIc
XXVIId
Pd/C-H2-100 psi, 50 °C
Pd/C-H2-100 psi, 50 °C
H2N
XXXIIIc
XXXIIId